NORTH AMERICAN POLYELECTROLYTE PRODUCERS ASSOCIATION

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Danica Andrews
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RE: Comments on Draft NTP Technical Report 575 – Acrylamide (CASRN 79-06-1) [76 FR 3276; 2/14/11]

Dear Ms. Andrews:

The North American Polyelectrolyte Producers Association (NAPPA)[1] appreciates the opportunity to provide comments on the draft National Toxicology Program (NTP) Technical Report 575 – Acrylamide (CASRN 79-06-1), which is scheduled for review by the NTP Technical Reports Peer Review Panel at a meeting on April 5, 2011 (76 FR 8741; February 15, 2010). The members of NAPPA are major North American manufacturers and importers of synthetically produced coagulants and flocculants, which are generically referred to as polyelectrolytes. Polyacrylamides are a significant class of these polyelectrolytes and NAPPA members produce both polyacrylamides and also the acrylamide monomer and as such have significant interest in this proceeding.

To assist with its review of the study report, NAPPA retained Dr. Joseph Haseman, formally a biostatistician at the NTP and previously involved with the interpretation of experimental results and preparing NTP Technical Reports. As noted in the attached report, Dr Haseman highlights various specific tumors that should not be included as supporting the "clear evidence" carcinogenicity determination, including:

- pancreatic islet cell adenoma in male rats;
- clitoral gland carcinoma in female rats; and,
- Skin squamous cell tumors in female mice.

Dr. Haseman raises several significant issues relating to the historical control data that was used to evaluate the various tumors types. His attached report explains that:

> (i) Most of the studies used for historical controls are 20-23 years old, which seems to diverge from the traditional practice of using historical controls from studies that are approximately 5-10 years old;

1 Current members of NAPPA include Ashland Inc., BASF, Kemira Water Solutions, Inc., and Nalco Company.

(ii) None of the studies for rats (and only one for mice) are drinking water studies which raise questions about the appropriateness of use;

(iii) For unexplained reasons, recent NTP drinking water studies are not used; and,

(iv) There are circumstances where the historical control tumor rates reported appear to be simply incorrect.

Also, there appears to be serious questions about the levels of evidence calls for mammary gland fibroadenoma in female rats and mesenchymal skin tumors in female mice, when the more relevant historical control data are used.

In addition to the issues raised by Dr. Haseman, there are other issues that we encourage NTP and the Technical Reports Peer Review Panel to consider in reviewing the report, most notably the low survival of the animals in the control and treated groups. We found it rather surprising that only 35% of the control male rats survived until the end of the study. We are deeply concerned that the low survivability, (i.e., high mortality) in the control animals suggests that these animals were somehow compromised. Moreover, the high mortality in the control animals impacts the statistics and further complicates the statistical comparison of treatment and controls and as such whether the effects are appropriately associated with acrylamide exposure.

Given the various issues associated with the study report, NAPPA recommends that the NTP defer finalizing the report until the NTP is ready to finalize the bioassay report on glycidamide. As the NTP is well aware, the toxicology of acrylamide and glycidamide are interrelated given that acrylamide is metabolized to the more biologically active glycidamide.

NAPPA was surprised to see that the NTP elected to review the acrylamide bioassay results separate from the glycidamide study. It was our assumption that the NTP would have wanted to review the results from acrylamide and glycidamide together, given that FDA nominated both acrylamide and glycidamide for testing as a means to understand better the toxicology of acrylamide. As noted in the draft report:

Consequently, the FDA nominated acrylamide for evaluation by the NTP. Acrylamide was hypothesized to be a genotoxic carcinogen as a result of metabolic conversion to glycidamide, which reacts with DNA. Since the metabolic conversion occurs to a greater extent in mice as compared to rats, mice were hypothesized to be more exensitive than rats to the carcinogenic effects of acrylamide. To test these hypotheses and to provide data for meaningful risk assessments, studies were conducted to compare the extent and types of tumors in B6C3F1 mice and F344/N rats treated chronically with either acrylamide or glycidamide.

In fact, NAPPA believes that the evaluation of these compounds would be enhanced if there was one integrated study report that addressed both acrylamide and glycidamide. A combined study appears more appropriate to address the overall purpose of conducting these two bioassays, i.e., to provide data for meaningful risk assessment. As it currently stands, there is discussion of what will soon be outdated glycidamide data in the acrylamide bioassay report. NAPPA believes that the NTP would be well served to hold off on finalizing the acrylamide report until the results from the glycidamide study are available, which we understand is only a few months away.

Please let me know if we can provide any further clarification on the issues identified in these comments.

Sincerely,
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Robert J. Fensterheim
Executive Director